IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 71007/137/USGO

In re patent application of
Apurba BHATTACHARJEE *et al.*
Serial No. 08/230,402
Filed: April 20, 1994
For: VACCINE AGAINST GRAM-NEGATIVE BACTERIAL INFECTIONS

Group Art Unit: 1802
Examiner: H. Sidberry

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Steven M. Opal, M.D., declare that:

1. I am Associate Professor of Medicine at the Brown University School of Medicine, Providence, Rhode Island, 02810.

2. I have had over 12 years of experience with animal models of sepsis, and I was on a National Institutes of Health Consensus Panel that dealt with this subject. My curriculum vita is enclosed.

3. I am familiar with the content of the captioned patent application relating to a vaccine against gram-negative bacterial infections.

4. In particular, I am expert on the use of the neutropenic rat model in studies of potential therapies that have progressed to human clinical trials. In my opinion, there is no other animal model for sepsis for which such extensive correlations with clinical trials have been shown.

5. The neutropenic rat model used in the captioned invention has been used for many studies of other potential

vaccines that have progressed to human clinical trials. Several of these will be mentioned below.

5.1. The HA-IA monoclonal antibody administered at the onset of fever has been tested in the neutropenic rat; the antibody was not effective. Clinical trials with this anti-lipid A antibody have also been carried out; they were also are negative, as predicted from the animal model.

5.2. Another anti-lipid A antibody, E5, was tested in the neutropenic rat model; 45% of the 24 animals tested survived. Addition of the bactericidal antimicrobial agent, ciprofloxacin, remarkaably improved the survival rate to 77% of 22 animals tested. Although initial clinical trials with this antibody were inconclusive, clinical trials with this reagent are still in progress. See also, Romulo *et al.*, *J. Infect. Dis.*, 167:126 (1993); copy enclosed as Exhibit A.

5.3. Another reagent, BPI, was tested in this neutropenic rat model in the form of BPI/LBP fusion protein. A survival rate of 60% (9 of 15) was observed, which is considered highly protective. In part based on these studies with the neutropenic rat model, the BPI reagent is in clinical trials for the treatment of meningococcemia, ischemia-reperfusion injury, hemorrhagic states, and in patients undergoing partial hepatectomy.

5.4. A fourth reagent, IL-1 receptor antagonist (IL-1a), was tested in the neutropenic rat model. The results demonstrated a 27%-37% protective efficiency. As a result, the reagent has progressed to clinical trials. It is revealing that the protective efficiency of IL-1a in the clinical trials of patients with established gram-negative shock was 26%, which is very similar to the results found in applicants' neutropenic rat model.

6. In addition, my laboratory team has received many requests from pharmaceutical companies to use the neutropenic rat model to test their candidate vaccines. These companies would not be making these requests were they not convinced of the predictive value of our rat model.

7. While no one animal model sepsis reproduces precisely the clinical picture of sepsis in man, in my expert opinion the results of treatment observed in this animal model are reflected in the degree of survival observed in clinical studies.

8. The examiner's assertion that it is not clear if the neutropenic rat is an art-recognized animal model for testing vaccines against gram-negative bacteria and LPs-mediated pathology is simply not correct. As I noted above, there is no other animal model of sepsis for which such extensive correlations with human clinical trials has been shown. In my opinion the neutropenic rat is the art-recognized animal model for gram-negative sepsis studies.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Steven M. Opal, M.D.

Date